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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/995,452	BENVENISTY ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,11-17,57-61,65-68 and 71-74* is/are pending in the application.

4a) Of the above claim(s) *57 and 58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,11-17,59-61,65-68 and 71-74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' Amendment and Response, filed 4/4/08, has been entered. Claims 1, 7, 11, 65-67 are amended; claims 71-74 are newly added; claims 8, 9, 69 and 70 are cancelled; claims 57-58 are not entered; claims 1-7, 11-17, 57-61, 65-68, 71-74 are pending and under current examination.

Claim Objections

The objection of claims 67, 69, 70 is withdrawn in view of Applicants' amendment to the claims.

Claim Rejections - 35 USC § 112

The prior rejection of claims 7 and 66 is withdrawn in view of Applicants' amendment to the claims which now recite that the transfection reagent is a linear polymer of ethyleneimine.

The prior rejection of claims 1-6, 8, 9, 11-17, 59-65, 67-70 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for new matter is withdrawn in view of Apps' amendment to the claims which now are limited to a cationic non-lipid polymer.

The prior rejection of claims 1-9, 11-17, 59-70 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of Applicants' amendments to the claims.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7, 11-17, 59-61, 65-68, and newly added claim 71 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description

requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a **new matter** rejection.

37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

Applicants' have now amended the claims to recite that the transfection efficiency is great than that obtainable by means of electroporation using a single 625 V/cm pulse at room temperature. This amendment to the claims constitutes new matter. In Applicants' response on pages 18-19, Applicants' discuss the Thomas publication, and electroporation used in this publication (additionally citing the Promega Biotech X Cell 2000), where Applicants point to using a single, 625 V/cm pulse at room temperature.

The phrase "using a single 625 v/cm pulse at room temperature" introduces new matter into the as-filed disclosure because of the following reasons:

1. Thomas discusses electroporation in murine ES cells. There is no contemplation in the as-filed disclosure of achieving greater efficiency of transfection using a cationic non-lipid polymer versus the conditions taught by Thomas (for murine ES cells) in the context of human embryonic stem cells, which is the instantly claimed invention.

2. There is no contemplation in the as-filed disclosure that the electroporation conditions, as taught by Thomas, are the same conditions that are used in electroporation techniques for human ES cells. The citation from Thomas merely recites what is used in murine ES cells, but provides no nexus for conditions used in human ES cells.

To the extent that the claimed compositions and/or methods are not described in the instant disclosure, claims 1-7, 11-17, 59-61, 65-68, 71 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not

described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described.

MPEP §2163.06 notes:
If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981).

MPEP §2163.02 teaches that:
Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application.

MPEP §2163.06 further notes:
When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure. (Emphasis added).

Enablement

Claims 1-7, 11-17, 59-61, 65-68 and newly added 71 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is maintained for reasons of record, advanced in the prior Office action, mailed 10/4/07.

Applicants' Arguments. Applicants argue that the present specification discusses electroporation techniques and that in murine ES cells, electroporation was found to be the method of choice for introducing foreign DNA into ES cells. Applicants provide the Thomas reference and state that this reference shows that the cells and vector were exposed to a single, 625 v/cm pulse at room temperature. Applicants further state that the Thomas reference has been incorporated by reference and that these conditions have now been physically inserted into the present specification in order to quantify the preferred means of electroporation. Thus, Applicants argue that this does not introduce new matter, but merely inserts what was previously incorporated. Applicants argue that the amendment to the claims with the limitation of 625 v/cm pulse at room temperature obviates the prior rejection and that the claims are now enabled.

Response to Arguments. These arguments have been considered, but are not persuasive. Although Applicants' amendment to the specification to more specifically include electroporation conditions taught by Thomas does not constitute introduction of new matter into the specification, this amendment does not provide an enabling disclosure for the claims. In particular, Thomas only discusses electroporation in the context of mouse ES cells. There is no teaching in Thomas to suggest that these conditions are used in human ES cells, which are instant claimed. Additionally, the specification provides no guidance to show that the methods and conditions taught by Thomas were used in the electroporation techniques on the hES cells of the claimed invention, or that if these electroporation conditions were used, that the resultant efficiency was compared to hES cells transfected with Exgen, *and* showed that the transfection efficiency using Exgen was greater transfecting hES cells using Thomas' techniques and conditions. In short, there is no nexus between what the transfection techniques and results taught by Thomas in mouse ES cells and the transfection of hES cells of the instant invention. This citation does not provide enablement for the claimed invention.

The prior rejection of record is maintained for the reasons set forth in the previous action.

Thus, the claims as written provide no specific parameter with which to compare the other transfection reagents' relative transfection efficiency. There is no guidance provided by the specification that a single, 625 V/cm pulse at room temperature was used to transfect the human ES cells in the electroporation techniques of the instant invention. Therefore, the specification provides no specific guidance for the transfection efficiency of using a single, 625 V/cm pulse at room temperature, there is no guidance to show that this would result in a transfection that is less than that achieved by utilizing ExGen. It is further noted that Applicants' only have support showing that ExGen provides transfection efficiency greater than means of electroporation, however, because the means of electroporation has not been defined, the Examiner cannot ascertain the proper scope of enablement, with regard to the parameters that are used to compare the two transfection methods. Accordingly, one of skill in the art would have had to practice undue experimentation to determine the specific, untaught parameters of electroporation, and then compare the other transfection reagents' relative transfection efficiency to these unknown parameters.

Claim Rejections - 35 USC § 103

The following rejections have been **withdrawn** in view of Applicants' amendment to the claims which now require that the transfection efficiency be greater than that obtainable by means of electroporation using a single 625 V/cm pulse at room temperature:

The rejection of claims 1-4, 6, 8, 9, 11-16, 36, 59-61, 65, 67-70 over Smith when taken with Ritter.

The rejection of claims 1-4, 6, 9, 11-13, 15, 16, 65, 67-70 over Smith *et al.* when taken with Gibco BRL catalog (p. 350, 1992, cited previously).

The rejection of claims 5 and 14 over Smith when taken with Ritter further in view of Myers *et al.*

The rejection of claim 17 over Smith when taken with Ritter further in view of Pascolo *et al.* (cited previously).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 72-74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith (**U.S. Pat. No.** 6,146,888, Reference AL of Applicants' Information Disclosure Statement, filed 3/26/03, cited previously) when taken with US Pat. No. 6,153,597 (Blanche *et al*, November 28, 2000). *This is new ground of rejection, necessitated by Applicants' amendment to the claims.*

The claims are directed to methods of altering gene expression in human embryonic stem cells, without affecting the pluripotent character by introducing a

polynucleotide into the population of hES cells by transfection in the presence of transfection reagent that is a linear polymer of polyethyleneimine.

Smith teaches the generation of genetically modified stem cells. The stem cells include both unipotential and pluripotent stem cells, embryonic stem cells, etc. See col. 2, lines 12-15. Smith teaches that the cells can contain a selectable marker which is capable of differential expression in stem cell and cells other than the desired stem cells, wherein the differential expression of the selectable marker results in preferential isolation and/or survival and/or division of the desired stem cells. They teach that the term "animal cell" embraces all animal cells, including human cells. See col. 2, lines 1-11. In particular, Smith teaches that a positive selectable marker or a negative selectable marker may be used in transfecting the cells. For example, a foreign gene, a cellular gene, or an antibiotic resistance gene, such as neomycin. See col. 2, lines 25-29. They further teach that various means of introducing the selectable marker may be employed, such as transfection, viral vector, lipofection, or by electroporation. See col. 2, lines 61-64. Therefore, Smith envisions transfection of various types of stem cells, including human embryonic stem cells. However, Smith do not teach the polynucleotide is transfected in the presence of a linear polymer of polyethyleneimine.

However, prior to the time of the claimed invention, the '597 patent teaches various compositions that are useful for nucleic acid transfection techniques. In particular, the reference teaches that linear polyethyleneimine (PEI) has an entirely advantageous property. See Col. 5, lines 25-45. See also, claims 1 and 5.

Accordingly, in view of the combined art, it would have been obvious for the ordinary skilled artisan to modify the transfection techniques of human ES cells, as suggested by Smith, and utilize a linear PEI, as taught by the '597, with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make this modification in view of the '597's teaching that PEI has is advantageous in transfection. Additionally, one of ordinary skill in the

art would have been readily knowledgeable in various techniques of transfection because these techniques would have been part of the ordinary capabilities of one skilled in the art. One of skill in the art would have recognized that there are many different art-recognized ways of transfecting a cell, and that the '597 provides guidance for using PEI. Thus, utilizing PEI would reasonably predictably result in the transfection of an hES cell.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (571)272-0736. The examiner can normally be reached on 9-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Thaian N. Ton/
Primary Examiner, Art Unit 1632